Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016

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The current Zika virus outbreak and its potential severe health consequences, especially congenital fetal syndrome, have led to increased concern about sexual transmission, especially in pregnant women and women of reproductive age. Here we report a case of Zika virus sexual transmission, likely male-to-female, in a totally asymptomatic couple.

Zika virus (ZIKV) is a mosquito-borne flavivirus transmitted by Aedes species [1,2]. It is also the first flavivirus known to be sexually transmittable between symptomatic patients [3-6]. We here report a ZIKV sexual transmission in a couple returning from Martinique, whereby both partners were asymptomatic.

**Description of cases**

A couple wishing to have children was referred to our Assisted Reproduction Treatment (ART) centre for in vitro fertilisation with donor semen (IVF-D), as the male partner had non-obstructive azoospermia. The couple presented for a first consultation in early February 2016 in preparation of an IVF-D cycle scheduled two months later. Until this time, they had planned to spend a two-week holiday in early March in the French overseas department and region of Martinique, which is an epidemic area for ZIKV [7].

On the day before the first consultation, guidelines issued by the French governmental agency regulating ART, had been released concerning ZIKV. In the case of the couple, these guidelines recommended that both partners be tested for ZIKV RNA by reverse transcription-polymerase chain reaction (RT-PCR) in blood and urine samples at least 28 days after they came back from Martinique [8]. In addition, at the same occasion and according to the guidelines, samples of the man’s seminal plasma and sperm cell suspension obtained after sperm preparation on gradient were also to be tested for ZIKV RNA by RT-PCR [8]. The couple was thus informed that the IVF-D cycle would be delayed and an appointment for the ZIKV RNA tests was scheduled 39 days after their return from the holiday (Figure).

Virological diagnosis was performed as previously described [3]. The woman tested positive for ZIKV RNA by RT-PCR in blood (i.e. serum) and urine samples. The man tested negative for ZIKV RNA in blood, but positive in urine and seminal plasma. Sperm cell suspension was not tested for ZIKV, as he was azoospermic. Serological analysis for the man indicated the presence of anti-ZIKV IgM (absence of anti-dengue IGM) and anti-flaviviruses IgG. At the time of the consultation and during the following week, both partners reported having no clinical symptoms of ZIKV infection during and after their stay in Martinique (i.e. no fever, cutaneous manifestation, arthritis, nor myalgia).

As *Ae. albopictus* and *Ae. aegypti* are not established in Brittany where the patients lived, the hypothesis of a local vector-borne infection was excluded. Due to the absence of clinical symptoms, the probable date of exposure to ZIKV could not be determined from the incubation period range. Instead, we used data from a systematic review of the time of viral clearance estimating that 5% of cases will have no detectable virus in the blood by 2.4 days after infection and 95% by 18.9 days [9]. The results of the blood tests, whereby the man tested negative for the virus, while the woman tested positive, pointed to him having been infected before her. The most likely period of exposure to ZIKV for the man was during his stay in Martinique. The woman was found to be viraemic in blood 39 days after her return, which if she had been infected at any time during the holiday trip would correspond to at least 20
days longer than the maximal time of viral clearance (Figure). These data, associated with the detection of ZIKV RNA in the man’s semen, support the hypothesis of ZIKV sexual transmission from the man to the woman between day 21 and day 36 after their return from Martinique. The couple reported having several unprotected sexual intercourses after their return.

**Background**

ZIKV is an emerging flavivirus currently responsible for a major outbreak in different areas of the world including for example South America, as well as islands of the Caribbean and the Pacific [7]. In addition to the vector-borne transmission of the virus by *Ae. aegypti* or *Ae. albopictus*, evidence of sexual transmission has been reported between symptomatic patients, from men-to-women or from men-to-men [3-6]. The interval between the onset of symptoms in the man and his partner has been observed to vary from 4 to 44 days [10]. Recently published data show a higher incidence of ZIKV infection in women of reproductive age in Brazil, suggesting a potential role for sexual transmission in the outbreak dynamic [11]. Knowledge on the maximum delay for possible sexual transmission from the time of infection, as well as knowledge of possible transmissions from asymptomatic infected individuals, are of real interest for public health in terms of establishing control measures, improving surveillance to detect the emergence of ZIKV in areas with no current circulation but where *Aedes* is established, and in terms of understanding the outbreak dynamic.

**Discussion and conclusions**

The finding in our study of a likely man-to-woman sexual transmission of ZIKV between two asymptomatic cases coincided with systematic virological testing in the context of ART. To date, all reported sexual transmissions implicated an index case with symptoms of ZIKV infection, either during a stay in an epidemic area or during the 2 weeks after return from such an area [3-6,10].

As up to 80% of patients infected with ZIKV remain asymptomatic, the level of sexual transmission could play a more important role than expected in the overall dynamic of ZIKV circulation [12]. This unapparent risk of transmission is of concern for pregnant women and women considering pregnancy, and highlights the need to reinforce the counselling and recommendations given to men travelling to epidemic regions and having sex with women of reproductive age. The possible sexual transmission from asymptomatic cases also increases the risk of emergence of ZIKV in Europe in areas where *Ae. albopictus* and *Ae. aegypti* are present.

ZIKV sexual transmission has been reported to occur up to 41 days after the onset of symptoms of the index case and ZIKV RNA has been detected in semen samples at 62 days post-symptom onset [10,13]. Issues related to viral presence and load in semen have been recently highlighted for Rift Valley fever virus and Ebola virus [14,15], whereby questions on the potential consequences have been raised for Ebola virus, as its long-lasting persistence has been shown in semen of survivors [15]. Whether the seminal level of ZIKV RNA follows the same slow decreasing pattern than Ebola virus is not known, but can be expected.

Crucial questions remain to be addressed regarding ZIKV sexual transmission. First, the prevalence of ZIKV persistence in semen needs to be clarified in large epidemiological studies. Second, describing the duration of virus persistence in semen and the dynamics of RNA viral load in semen will help decipher the virus pathophysiological cycle in the male genitourinary tract. These data are of utmost importance in order
to determine the overall probability of ZIKV sexual transmission.

Conflict of interest
None declared.

Authors’ contributions
Wrote the manuscript: TF, SM; performed laboratory investigations: MM, IL-G; managed the patients and lead the epidemiological investigation: BH, TF, SM, CS, PB; revised the manuscript: BH, IL-G

References
11. Coelho FC, Durovni B, Saraceni V, Lemos C, Codeço CT, Camargo S, et al. Sexual transmission causes a marked increase in the incidence of Zika in women in Rio de Janeiro, Brazil. Available from: http://biorxiv.org/content/early/2016/05/26/055459

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